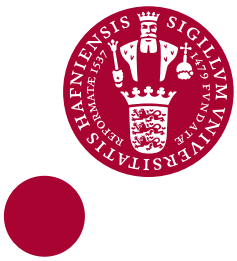

Risk factors for Staphylococcus aureus bacteremia in patients with rheumatoid arthritis and incidence compared with the general population

Protocol for a Danish nationwide observational cohort study

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Risk factors for *Staphylococcus aureus* bacteremia in patients with rheumatoid arthritis and incidence compared with the general population: protocol for a Danish nationwide observational cohort study

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ABSTRACT

Introduction *Staphylococcus aureus* bacteremia (SAB) is an invasive infection with high mortality and morbidity. Rheumatoid arthritis (RA) is associated with increased risk of infections due to the disease per se and the use of antirheumatic treatments. Few minor studies have previously investigated risk of SAB in patients with RA and indicated increased risk compared with the general population. This nationwide observational study aims to investigate incidence of and risk factors for SAB in adult patients with RA compared with the general population. The effect of disease characteristics (eg, joint erosions, disease duration and activity), different antirheumatic treatments and smoking on SAB risk will be evaluated.

Methods and analysis All adults (>18 years of age) alive and living in Denmark in 1996–2017 will be identified in The Danish Civil Registration System. Incident patients with RA are identified in the Danish National Patient Registry (DNPR) and the nationwide rheumatology registry, DANBIO, in which information on, for example, antirheumatic treatments, disease characteristics and smoking is collected prospectively in routine care. Information on comorbidities, invasive procedures and prescribed drugs are identified in the DNPR and in The Register of Medicinal Product Statistics. Socioeconomic status is evaluated in national registers on income and education. Incident cases of first-time SAB are identified in The Danish National SAB Database. All registers are linked on an individual level by unique civil registration numbers. Incidence rates and incidence rate ratios will be analysed using Poisson regression models and the impact of possible risk factors will be evaluated.

Ethics and dissemination All data will be handled in accordance with the General Data Protection Regulation (EU) 2016/679. No ethical approval is necessary in Denmark when handling registry data only. The results will be presented in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology initiative in international peer-reviewed journals and at medical conferences.

Strengths and limitations of this study

- We will identify patients with incident rheumatoid arthritis (RA) (the exposure of interest) and *Staphylococcus aureus* bacteremia (SAB) (the outcome of interest) in a nationwide cohort study including all adult Danes (1996–2017) identified by national registries.
- Nationwide medical databases are used to assess SAB incidence rates in the RA cohort and in the general population and to evaluate the impact of RA disease characteristics and treatments on SAB risk.
- We will assess the impact of possible confounding factors (eg, comorbidities, surgeries, prescriptions and socioeconomic factors) by linkage of national registries.
- Misclassification of RA and of SAB may occur, resulting in underestimation of the SAB incidence and potentially leading the relative estimates towards the null.
- Data on lifestyle factors (alcohol and smoking) are available in the RA cohort but lack in the background population. Other factors as illicit drug use, *S. aureus* nasal carriage and presence of central or peripheral vascular catheters are generally unavailable.

Trial registration number NCT03908086.

INTRODUCTION

Staphylococcus aureus bacteremia (SAB) is an invasive infection with an estimated overall annual incidence rate (IR) of 36/100 000 person-years.[1] Mortality is high (20%–30%) and morbidity significant due to the frequent occurrence of secondary infections, for example, endocarditis, spondylitis, septic arthritis and prosthetic joint infections.[1–3]

SAB among adults is more common in men, in elderly individuals and in patients with comorbidities such as diabetes mellitus, cancer, hemodialysis, HIV infection, heart failure, liver disease, alcohol abuse and intravenous drug abuse.[1 4–7] Biofilm of *S. aureus* can form on implanted foreign bodies as prosthetic joints, prosthetic heart valves and intravascular devices serving as an infective focus of SAB.[8] Furthermore, *S. aureus* nasal carriage, surgical procedures, treatment with immunosuppressive drugs (including glucocorticoids) and low-socioeconomic status have been associated with increased risk of SAB[4 9–11] whereas treatment with statins and trimethoprim/sulfamethoxazole (TMP/SMX) have been associated with a decreased risk.[12–14]

Rheumatoid arthritis (RA) is a chronic autoimmune joint disorder that affects 0.5–1% of the population.[15] Genetic factors, female sex, smoking and low-socioeconomic status increases the risk of RA.[15–17] Joint inflammation can lead to joint destruction, and patients with RA more often have joint replacements than the general population.[18] RA is associated with an increased risk of other chronic diseases such as diabetes mellitus and cardiovascular disease.[19 20]

Patients with RA are at increased risk of infections affecting, for example, lungs, joints and bones.[21 22] This has been observed even before the era of widespread use of the immunosuppressing disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids, indicating that the immune defense is compromised in patients with RA irrespective of treatment.[23 24] Furthermore, high RA disease activity has been reported to increase the risk of infections.[25] Antirheumatic treatments such as biologic DMARDS (bDMARDs, eg, tumour necrosis factor alpha inhibitors (anti-TNFs))[26–28] and the newer targeted synthetic DMARDs (tsDMARDs, eg, tofacitinib and baricitinib)[29 30] as well as glucocorticoids[22 31–33] have been found to be associated with increased risk of infections in patients with RA. Recent studies have, however, reported that the risk of serious infections using bDMARDs is minimal/insignificant suggesting a successful change in management of patients through screening for infections prior to start of bDMARDs, prophylactic measures as vaccines and treating infections early.[27 34]

Patients with RA are likely at increased risk of SAB due to the RA disease per se (altered immunological response to infections due to systemic inflammation and local inflammation in joints leading to erosions), or due to the antirheumatic treatment and the prevalence of joint prostheses and comorbidities. Despite the severity of SAB, the incidence and risk factors for SAB among patients with RA are poorly investigated. Two previous studies of SAB incidence in adult patients with RA, both characterised by few events of SAB in patients with RA, reported incidence rate ratios (IRRs) of 2.6 (95% CI 1.8 to 3.7)[4] and 9.2 (95% CI 1 to 20)[7] compared with the background population. One small nested case–control study reported indwelling central venous catheters (OR 15.97, 95% CI 5.09 to 50.10) and congestive heart failure (OR 2.89, 95% CI 1.26 to 6.63) as risk factors for RA patients being hospitalised with SAB. The study found no association between neither conventional synthetic DMARDs (csDMARDs), bDMARDs, glucocorticoids nor prosthetic joints and SAB.[35] However, their comparisons were RA patients hospitalised for other reasons than SAB. These patients were likely at higher risk of SAB than RA patients in general, which may have biassed the relative estimates towards no association. Thus, the evidence gap regarding SAB in patients with RA is substantial: the incidence of SAB in the RA population is unknown and there is insufficient knowledge on risk factors for SAB.

This protocol presents a nationwide observational cohort study of SAB focusing on IRs and risk factors in adult patients with RA compared with the adult general population. The study is expected to become the largest and most detailed of its kind due to the availability of unique national registries of microbiologically verified cases of SAB and of RA patients' demographics, antirheumatic treatment, disease characteristics and disease activity including patient-reported outcomes, combined with the possibility of linking to other national registries with information on, for example, comorbidities (hospital contacts and prescriptions) and socioeconomic parameters (education and income). Further, the study is expected to conclude whether different antirheumatic treatments are associated with different risk of SAB in the RA population.

We hypothesise that patients with RA are at increased risk of SAB compared with the background population. We expect that higher age, male sex, glucocorticoid use and joint prostheses increase this risk in both patients with RA and the background population, and we hypothesise that additional RA disease-specific factors (eg, high disease activity, presence of joint erosions, long disease duration, DMARD treatment and smoking) might be associated with higher risk in patients with RA. The objectives of the study are to (1) assess the IRs and IRRs of SAB in patients with RA compared with the general population; (2) explore the significance of age, gender, glucocorticoid use and prosthetic joints on SAB risk in patients with RA compared with the general population; and (3) identify RA disease-specific risk factors for SAB within the RA cohort and assess the effect of smoking on SAB risk in the RA cohort.

METHODS AND ANALYSIS

Study design and population

Nationwide observational cohort study of SAB incidence and risk factors in adult patients with RA and in the general adult population. The population consists of all Danish inhabitants aged 18 years or more, alive and living in Denmark in the period from 1996 until 2017 as identified by the Danish Civil Registration System (CRS) (table 1). Individuals with one of the following prior to start of follow-up will be excluded: (1) SAB (the outcome

Table 1 Data sources, Danish national registries

The Danish Civil Registration system	Established in year 1968. All persons alive and living in Denmark are registered for administrative use. Includes complete information on civil registration number, name, gender, date of birth and continuously updated information on vital status, marital status and place of residence (including immigration and emigration).[41]
The Danish National Patient Registry	Diagnoses listed according to the International Classification of Diseases (ICD) codes from all hospital admissions (from 1977) and outpatient activities (from 1995) in the form of the 8th revision of the ICD (ICD-8) until 1994 and the 10th revision (ICD-10) thereafter. Contains information on surgeries and other procedures performed at hospitals. The register is practically complete.[42]
The Danish Rheumatology Database, DANBIO	Initiated in year 2000. Danish national clinical quality registry of rheumatologic patients treated with biologics. In 2006, it became mandatory to register all newly diagnosed RA patients regardless of treatment. >30 000 patients with RA have been registered (unpublished data). Contains information on for example, ICD-10 diagnosis code of inflammatory rheumatic disease, date of diagnosis, symptom duration, auto-antibody status of rheumatoid factor (RF) and anticitrullinated peptide antibodies (ACPA), current and previous treatment with biologic and synthetic disease-modifying antirheumatic drugs (DMARDs), treatment with glucocorticoids (injection, oral), X-ray results (hands and feet) and prospectively collected disease activity measures including C reactive protein (CRP) and patient-reported outcomes. Smoking, alcohol consumption and body mass index (BMI) is also registered.[43]
The Danish National *Staphylococcus aureus* Bacteremia Database	The nationwide registration of *S. aureus* bacteremias in Denmark since 1957 carried out by the Staphylococcal Laboratory at the Statens Serum Institut (SSI) for surveillance purposes. Linked to civil registration numbers since 1992. The regional microbiology departments send isolates on a voluntary basis. Has a high degree of completeness and >90% of strains isolated from Danish blood cultures are referred to SSI for typing (detection *S. aureus* protein A (SPA) type) and antibiotic susceptibility testing.[44]
The Register of Medicinal Product Statistics	Information on all prescriptions dispensed from pharmacies has been recorded from 1995 including the anatomical therapeutic chemical class (ATC class), strength, package size, number and date of dispensed prescription.[45]
The Population's Education Registry (PER)	Information on highest attained education. In 2008 PER included 96.4% of the Danish population between 15 and 69 years of age.[46]
The Income Statistics Register	Initiated in 1970. Contains information on the income and its composition (eg, salary, taxes and public transfer payments) on an individual level as registered by the Tax Administration's registry.[47]

All national registries can be linked on an individual basis using the civil registration number administered at birth or immigration.[41]

of interest) and (2) a diagnosis of RA (the main exposure of interest)

Exposure

RA is the main exposure of interest. A cohort of incident cases of RA will be identified based on DANBIO and the Danish National Patient Registry (DNPR). Individuals registered with one of the following International Classification of Diseases codes in its 10th revision (ICD-10) in DANBIO are considered patients with RA: M05.9 (RA seropositive), M06.0 (RA seronegative) and M06.9 (RA unspecified). Furthermore, in the DNPR individuals with ≥2 registrations from rheumatology departments with one of the mentioned ICD-10 codes (including also M05.8 (other types of RA), not used in DANBIO) or the ICD-8 code 712.39 (arthritis rheumatoides alia et non specificata), within a period of 90 days are considered patients with RA. This method has previously been validated with high degree of validity (positive predictive value ≈80%) and completeness.[36]

Outcome/event

The outcome of interest is incident first-time SAB as identified in the Danish National *S. aureus* Bacteremia Database. SAB relapses/reinfections will not be included. SAB events will be labelled 'hospital-acquired' (HA SAB) if the first blood culture with *S. aureus* is obtained 48 hours or more after admission to a hospital and non-hospital acquired (non-HA SAB) if it is obtained <48 hours after admission. The non-HA SAB may be further subdivided into healthcare-associated SAB (HCA SAB) and community-acquired SAB (CA SAB) based on whether the patient has had recent hospital contact or not. Cases of SAB will further be classified with regards to the causative microorganism as cases of methicillin-resistant *S. aureus* (MRSA) SAB or methicillin-sensitive *S. aureus* (MSSA) SAB.

Follow-up

Follow-up starts at 31 December 1996, an individual's 18th birthday, or at the date of immigration, whichever comes last. Individuals are followed up until first-time SAB, emigration, death or 31 December 2017, whichever comes first. Incident patients with RA contribute with person-years in the RA cohort following diagnosis and until the end of follow-up. The remaining individuals contribute person-years in the general population cohort. RA patients diagnosed after start of follow-up will contribute person-years in the general population cohort until date of RA diagnosis and in the RA cohort thereafter.

Covariates

Information on diseases known to affect SAB risk (eg, diabetes mellitus and hemodialysis) and use of prescription medications (eg, glucose-lowering medication and TMP/SMX) will be obtained prior to baseline and during follow-up from the DNPR and the Register of Medicinal Product Statistics. Some conditions (eg, diabetes mellitus and prosthetic joint insertion) leaves the subject in 'forever risk' from the date of diagnosis/operation and until the end of follow-up. Other incidents, as invasive surgical procedures and dialysis procedures are considered temporary risk factors, and subjects are considered 'at risk' of one of these in 90 days after the procedure date. Patients with cancer (except non-melanoma skin cancer) are considered at risk until 5 years after the last registration of a cancer diagnosis in the DNPR. Socioeconomic status will be evaluated by the highest attained educational level identified by the Population's Education Registry and by the yearly average personal income level (3 years back) identified by the Income Statistics Register.

To allow for evaluation of RA specific risk factors, information specific to RA patients will be identified in DANBIO prior to and during follow-up (table 2). Information on smoking habits is systematically collected annually in DANBIO and has a high degree of completeness.[37] DANBIO is the main source of information on antirheumatic treatments since, in Denmark, some drugs are administered from the hospital departments without prescription (bDMARDS, subcutaneous methotrexate, leflunomide and injections with glucocorticoids) and hence not registered in the Register of Medicinal Products Statistics. A recent audit in DANBIO found a coverage of 98% for bDMARDs.[38] Information on glucocorticoid use will be identified in both DANBIO and the Register of Medicinal Products Statistics (table 2).

Expected number of events

When identifying incident RA cases in the DNPR and DANBIO as described above, we expect to identify approximately 500 SAB cases in the RA cohort. This is based on data from the annual report from The Danish National SAB Database.[1] Thus, from year 1996 until 2017 ≈30 000 SAB cases were reported whereof, in the last years, ~5% (4.7%–6.2%) occurred in patients with comorbid 'rheumatic diseases', corresponding ≈1500 cases in total (5% of 30 000). The expected number of events is based on the conservative assumption that one-third of these patients will be incident patients with RA.

Since we have more detailed information on RA patients that have been followed in DANBIO (eg, smoking, disease activity, joint erosions and so on) compared with RA patients identified in the DNPR, we will consider limiting exposure to only RA according to DANBIO if the number of events is large enough for meaningful statistical analysis. In this case, the study period will be limited accordingly to 2006 and onwards.

Data analysis plan

The exact data analysis plan depends on data availability and number of events. IRs of SAB in the RA and in the general population cohorts will be calculated and multivariable Poisson regression models will be used to estimate IRRs. IRRs will be presented crude (adjusted for age, sex and calendar year) and further adjusted for potential confounders. We will use a dynamic statistical method to assess the impact of an RA diagnosis while accounting for other possible and known risk factors (eg, socioeconomic status, comorbidities and dialysis procedures). The Lexis macro will be used to split follow-up time according to calendar time, age and exposure status (eg, comorbidities and socioeconomic status). Comorbidities will be entered as time-varying variables in the model.

The impact of risk factors for SAB in patients with RA compared with the general population will be analysed as events in the exposed time-period compared with events in the unexposed time-period using the multivariable Poisson regression model. If statistical interaction is observed between RA and any of the potential or known risk factors, stratified analyses will be performed.

The impact of possible risk factors (antirheumatic treatment, disease duration, disease activity, joint erosions and smoking) for SAB among RA patients will be assessed. The number of covariates included in the final model will correspond the number of events in the RA population and will be prioritised according to a-priori assumption of clinical relevance. We plan to study the impact of different DMARD treatments as risk factors for SAB among patients with RA separately, alternatively grouped as for example, bDMARDs, tsDMARDs and csDMARDs.

Sensitivity analyses will include stratified analysis according to outcome defined as HA SAB, and non-HA SAB which can further be distinguished as HCA and CA SAB. The number of MRSA and MSSA SAB events in the RA and general population cohort will be presented. We do not expect the statistical power to allow us to perform separate analysis of risk factors for MRSA SAB due to an expected low number of cases.[1] Further sensitivity analysis will be performed to assess any difference in IR

Table 2 Characteristics of patients with RA according to the DANBIO registry

Variable	Description	Value
CDAI	Composite disease activity score of patient's and doctor's global assessment on a visual analogue scale	0.0–76.0
Disease duration	Time passed from RA diagnosis until the first-time SAB	Years
Erosive joint disease	X-rays of hands and feet registered before the first-time SAB	Erosions/no erosions/unavailable
Autoantibody status	ACPA and RF registered before SAB	Positive/negative/unavailable
Smoking	Smoking status registered as close to SAB as possible	Previous/current/never/occasional/unavailable
csDMARDs		
Methotrexate, sulphasalazine, hydroxychloroquine, leflunomide	Current user: use within 90 days before SAB Previous user: ever used >90 days prior to SAB Non-user: Never used Cumulated exposure: days on the drug (for current users)	Current/previous/non-user and cumulated exposure (days)
bDMARDs		
Anti-TNFs, abatacept, secukinumab, IL6 inhibitors, ustekinumab, apremilast	Current user: use within 90 days before SAB Previous user: ever used >90 days prior to SAB Non-user: never used Cumulated exposure: days on the drug (for current users)	Current/previous/non-user and cumulated exposure (days)
Rituximab	Current user: last dose of rituximab was given within 12 months prior to SAB Previous user: ever used Non-user: never used Cumulated exposure: total dose (both current and previous users)	Current/previous/non-user and cumulated exposure (mg)
tsDMARDs		
JAK inhibitors	Current user: use within 90 days before SAB Previous user: ever used more than 90 days prior to SAB Non-user: never used Cumulated exposure: days on the drug (for current users)	Current/previous/non-user and cumulated exposure (days)
Glucocorticoids (GCs)*		
Oral and injectable (intramuscular and intraarticular) GCs	Current user: use within 90 days before SAB Previous user: ever used >90 days prior to SAB Non-user: never used Cumulated exposure: will be calculated as prednisolone-equivalent dose for current users as described elsewhere[10]	Current/previous/non-user and cumulated exposure (mg)

*Use of GCs will be identified in both DANBIO and the Register of Medicinal Products Statistics.
CDAI, clinical disease activity index; IL6 inhibitors, interleukin-6 inhibitors (tocilizumab, sarilumab); JAK inhibitors, Janus kinase inhibitors (baricitinib, tofacitinib); RA, rheumatoid arthritis; SAB, *Staphylococcus aureus* bacteremia; anti-TNF, tumor necrosis factor inhibitors (adalimumab, golimumab, etanercept, certolizumab pegol, infliximab); bDMARDs, biologic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic DMARDS; tsDMARDs, targeted synthetic DMARDs.

between the RA cohort identified in DANBIO and the full RA cohort identified by both DANBIO and the DNPR. Missing data will be handled by appropriate statistical methods, for example, multiple imputations.

Data will be hosted and anonymised by Statistics Denmark and data will be processed using the statistical software SAS. Data access is expected in June 2019. Data analysis will start when access is obtained and is expected to end in January 2020.

Patient and public involvement

The study hypotheses and design were discussed with a trained patient research partner both in the very beginning of the brainstorming phase of the study and later when the study hypotheses were formed. The purpose was to secure that possible risk factors evaluated were also important from a patient perspective, for example, we agreed on risk associated with different treatments, disease duration and disease activity.

ETHICS AND DISSEMINATION

All data will be handled in accordance with the General Data Protection Regulation (EU) 2016/679. Data processing agreements are set up between all data processors and the data owner (the Capital Region of Denmark). Data handling and data processing agreements are approved by the Capital Region of Denmark. Access to data from The Register of Medicinal Product Statistics is approved by Sundhedsdatastyrelsen, data from DANBIO are approved by The Danish Clinical Registries (RKKP) and data from the Danish National SAB Database are approved by Statens Serum Institut. Statistics Denmark has authorised the research institution and granted permission to linkage of data based on a written application. No ethical approval is necessary in Denmark when handling registry data only. The results will be presented in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology initiative[39] as original articles in international peer-reviewed journals and at medical conferences. Both positive and negative results will be published.

FUTURE PERSPECTIVES

The outcome of SAB in patients with RA remains to be investigated in further detail. One study on the subject suggested that patients with RA are at increased risk of a fatal outcome after SAB and that multiple metastatic infections in joints and bones are common.[40] When the disease burden of SAB in Danish patients with RA has been established in the current study, we plan to perform further studies on outcome after SAB including all-cause mortality, incidence of secondary infections and frequency of recurrent SAB in patients with RA compared with non-RA patients. We plan to identify risk factors for poor outcome that can guide physicians in the evaluation of a SAB patient with comorbid RA.

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Contributors SSD conceptualised the study hypotheses. MLH, BG, MN, LBO, FM, TB and AP contributed with the further development of these and with the study design. SSD wrote the first draft of the paper, which was critically revised by the other authors.

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REFERENCES

1. Petersen A. Staphylococcus aureus bacteraemia cases in Denmark 2017, 2017. Available: http//www.ssi.dk/~/media/Indhold/DK - dansk/Smitteberedskab/Referencelaboratorier/Stafylokoklaboratoriet/SAB 2014.ashx 1–20
2. Mejer N, Westh H, Schønheyder HC, *et al*. Stable incidence and continued improvement in short term mortality of Staphylococcus aureus bacteraemia between 1995 and 2008. *BMC Infect Dis* 2012;12:260.
3. Stammler Jaliff B, Dahl-Knudsen J, Petersen A, *et al*. Outcome and reinfection after *Staphylococcus aureus* bacteraemia in individuals with and without HIV-1 infection: a case-control study. *BMJ Open* 2014;4:e004075.
4. Laupland KB, Ross T, Gregson DB. *Staphylococcus aureus* bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000-2006. *J Infect Dis* 2008;198:336–43.
5. Smit J, Søgaard M, Schønheyder HC, *et al*. Diabetes and risk of community-acquired Staphylococcus aureus bacteremia: a population-based case-control study. *Eur J Endocrinol* 2016;174:631–9.
6. Bassetti S, Battegay M. Staphylococcus aureus infections in injection drug users: risk factors and prevention strategies. *Infection* 2004;32:163–9.
7. Jacobsson G, Dashti S, Wahlberg T, *et al*. The epidemiology of and risk factors for invasive Staphylococcus aureus infections in Western Sweden. *Scand J Infect Dis* 2007;39:6–13.
8. Bhattacharya M, Wozniak DJ, Stoodley P, *et al*. Prevention and treatment of *Staphylococcus aureus* biofilms. *Expert Rev Anti Infect Ther* 2015;13:1499–516.
9. Wertheim HFL, Vos MC, Ott A, *et al*. Risk and outcome of nosocomial Staphylococcus aureus bacteraemia in nasal carriers versus non-carriers. *The Lancet* 2004;364:703–5.
10. Smit J, Kaasch AJ, Søgaard M, *et al*. Use of glucocorticoids and risk of community-acquired Staphylococcus aureus bacteremia: a population-based case-control study. *Mayo Clin Proc* 2016;91:873–80.
11. Oestergaard LB, Schmiegelow MD, Bruun NE, *et al*. The associations between socioeconomic status and risk of Staphylococcus aureus bacteremia and subsequent endocarditis – a Danish nationwide cohort study. *BMC Infect Dis* 2017;17:1–9.
12. Smit J, López-Cortés LE, Thomsen RW, *et al*. Statin use and risk of community-acquired Staphylococcus aureus bacteremia: a population-based case-control study. *Mayo Clinic Proceedings* 2017;92:1469–78.
13. Hughes WT, Kuhn S, Chaudhary S, *et al*. Successful Chemoprophylaxis for *Pneumocystis carinii* Pneumonitis. *N Engl J Med* 1977;297:1419–26.
14. Gurwith MJ, Brunton JL, Lank BA, *et al*. A prospective controlled investigation of prophylactic trimethoprim/sulfamethoxazole in hospitalized granulocytopenic patients. *Am J Med* 1979;66:248–56.
15. Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. *The Lancet* 2010;376:1094–108.
16. Bergström U, Jacobsson LTH, Nilsson Jan-Åke, *et al*. Pulmonary dysfunction, smoking, socioeconomic status and the risk of developing rheumatoid arthritis. *Rheumatology* 2011;50:2005–13.
17. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *The Lancet* 2016;388:2023–38.
18. Cordtz RL, Hawley S, Prieto-Alhambra D, *et al*. Incidence of hip and knee replacement in patients with rheumatoid arthritis following

the introduction of biological DMARDs: an interrupted time-series analysis using nationwide Danish healthcare registers. *Ann Rheum Dis* 2018;77:684–9.
19. Kokkonen H, Stenlund H, Rantapää-Dahlqvist S. Cardiovascular risk factors predate the onset of symptoms of rheumatoid arthritis: a nested case-control study. *Arthritis Res Ther* 2017;19.
20. Lindhardsen J, Ahlehoff O, Gislason GH, *et al*. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. *Ann Rheum Dis* 2011;70:929–34.
21. Doran MF, Crowson CS, Pond GR, *et al*. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum* 2002;46:2287–93.
22. Widdifield J, Bernatsky S, Paterson JM, *et al*. Serious infections in a population-based cohort of 86,039 seniors with rheumatoid arthritis. *Arthritis Care Res* 2013;65:353–61.
23. Baum J. Infection in rheumatoid arthritis. *Arthritis Rheum* 1971;14:135–7.
24. Rimoin DL, Wennberg JE, John E. Acute septic arthritis complicating chronic rheumatoid arthritis. *JAMA* 1966;196:617–13.
25. Weaver A, Troum O, Hooper M, *et al*. Rheumatoid arthritis disease activity and disability affect the risk of serious infection events in radius 1. *J Rheumatol* 2013;40:1275–81.
26. Lahiri M, Dixon WG. Risk of infection with biologic antirheumatic therapies in patients with rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2015;29:290–305.
27. Ramiro S, Sepriano A, Chatzidionysiou K, *et al*. Safety of synthetic and biological DMARDs: a systematic literature review Informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2017;76:1101–36.
28. Ruderman EM. Overview of safety of non-biologic and biologic DMARDs. *Rheumatology* 2012;51 Suppl 6(suppl 6):vi37–43.
29. Winthrop KL, Park S-H, Gul A, *et al*. Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. *Ann Rheum Dis* 2016;75:1133–8.
30. Cohen SB, Tanaka Y, Mariette X, *et al*. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. *Ann Rheum Dis* 2017;76:1253–62.
31. Richter A, Listing J, Schneider M, *et al*. Impact of treatment with biologic DMARDs on the risk of sepsis or mortality after serious infection in patients with rheumatoid arthritis. *Ann Rheum Dis* 2016;75:1667–73.
32. Crowson CS, Hoganson DD, Fitz-Gibbon PD, *et al*. Development and validation of a risk score for serious infection in patients with rheumatoid arthritis. *Arthritis Rheum* 2012;64:2847–55.
33. Dixon WG, Abrahamowicz M, Beauchamp M-E, *et al*. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case–control analysis. *Ann Rheum Dis* 2012;71:1128–33.
34. Aaltonen KJ, Joensuu JT, Virkki L, *et al*. Rates of serious infections and malignancies among patients with rheumatoid arthritis receiving either tumor necrosis factor inhibitor or rituximab therapy. *J Rheumatol* 2015;42:372–8.
35. Sams M, Olsen MA, Joshi R, *et al*. Staphylococcus aureus sepsis in rheumatoid arthritis. *Rheumatol Int* 2015;35:1503–10.
36. Ibfelt EH, Sørensen J, Jensen DV, *et al*. Validity and completeness of rheumatoid arthritis diagnoses in the nationwide DANBIO clinical register and the Danish national patient registry. *Clin. Epidemiol* 2017;9:627–32.
37. Glintborg B, Højgaard P, Lund Hetland M, *et al*. Impact of tobacco smoking on response to tumour necrosis factor-alpha inhibitor treatment in patients with ankylosing spondylitis: results from the Danish nationwide DANBIO registry. *Rheumatology* 2016;55:659–68.
38. Jensen D. V, Hetland ML, Svensson E, *et al*. DANBIO national årsrapport 2017, 2017. Available: https://danbio-online.dk/formidling/copy2_of_DANBIOrsrapport_2017.pdf
39. von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;147:573–8.
40. Joost I, Kaasch A, Pausch C, *et al*. Staphylococcus aureus bacteremia in patients with rheumatoid arthritis - Data from the prospective INSTINCT cohort. *J Infect* 2017;74:575–84.
41. Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–9.
42. Schmidt M, Schmidt SAJ, Sandegaard JL, *et al*. The Danish national patient registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–90.
43. Hetland ML, Krogh NS, Hørslev-Petersen K, *et al*. Using an electronic platform interactively to improve treatment outcome in patients with rheumatoid arthritis: new developments from the DANBIO registry. *Clin Exp Rheumatol* 2016;34(5 Suppl 101):S75–S78.
44. Benfield T, Espersen F, Frimodt-Møller N, *et al*. Increasing incidence but decreasing in-hospital mortality of adult Staphylococcus aureus bacteraemia between 1981 and 2000. *Clin Microbiol Infect* 2007;13:257–63.
45. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, *et al*. Data resource profile: the Danish national prescription registry. *Int J Epidemiol* 2017;46:798.
46. Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health* 2011;39(7 Suppl):91–4.
47. Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scand J Public Health* 2011;39(7 Suppl):103–5.